1/4/99

> d l24 5,6,10,11,12,20,43,42,41,38,37,36, bib ab

L24 ANSWER 5 OF 43 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 3
AN 1999:454690 BIOSIS
DN PREV199900454690
TI The cell cycle-regulating transcription factors **E2F-RB**
.
AU Brehm, A.; Miska, E.; Reid, J.; Bannister, A.; Kouzarides, T. (1)
CS (1) Department of Pathology, Wellcome/CRC Institute, Tennis Court Road, Cambridge, CB2 1QR UK
SO British Journal of Cancer, (July, 1999) Vol. 80, No. SUPPL. 1, pp. 38-41.
ISSN: 0007-0920.
DT Article
LA English

L24 ANSWER 6 OF 43 CAPLUS COPYRIGHT 2000 ACS
AN 1998:341586 CAPLUS
DN 129:36444
TI Transcription factor **E2F-Rb** protein fusions and and tissue-specific expression of **E2F-Rb** fusions in treatment of hyperproliferative diseases
IN Antelman, Douglas; Gregory, Richard J.; Wills, Kenneth N.
PA Canji, Inc., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9821228	A1	19980522	WO 1997-US21821	19971113
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9855899	A1	19980603	AU 1998-55899	19971113
EP 948520	A1	19991013	EP 1997-952238	19971113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, LT, LV, FI, RO				

PRAI US 1996-751517 19961115
US 1997-801092 19970214
WO 1997-US21821 19971113
AB Fusions of the transcription factor E2F and the retinoblastoma protein Rb are provided, along with methods of treatment of hyperproliferative diseases. 1-194- Or 1-286-E2F fused to 379-928-Rb protein contg. A-606, A-612, A-788, A-807, and A-811 substitution mutations repressed transcription from an E2-CAT reporter construct 50-fold while the Rb protein mutant itself repressed transcription only 10-12-fold. An adenovirus vector expressing these fusion proteins from an actin promoter inhibited proliferation of smooth muscle cells.

L24 ANSWER 10 OF 43 CAPLUS COPYRIGHT 2000 ACS
AN 1998:541965 CAPLUS
DN 129:242858
TI Toward an understanding of the functional complexity of the E2F and retinoblastoma families
AU Nevins, Joseph R.
CS Duke University Medical Center, Department of Genetics, Howard Hughes Medical Institute, Durham, NC, 27710, USA
SO Cell Growth Differ. (1998), 9(8), 585-593
CODEN: CGDIE7; ISSN: 1044-9523

AN 1998376895 MEDLINE
DN 98376895
TI Interaction of **E2F/Rb** family members with factor binding to co-repressor element on B-myb and E2F1 promoters.
AU Nakajima Y
CS Second Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Tokyo Medical and Dental University.
SO KOKUBYO GAKKAI ZASSHI. THE JOURNAL OF THE STOMATOLOGICAL SOCIETY, JAPAN, (1998 Jun) 65 (2) 172-88. Journal code: IQF. ISSN: 0300-9149.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Dental Journals
EM 199812
EW 19981204
AB The E2F transcription factor plays an important role in controlling the expression of genes required for cell cycle progression. The transcription of a number of these genes, including E2F1 and B-myb, is repressed in G0/early G1 at E2F DNA binding sites mediated by interaction of E2F with the Rb family member proteins. It was shown that a corepressor element CHR, which was originally identified in the B-myb promoter, is also responsible for the repression of the E2F1 promoter. The mutation of the CHR element adjacent to E2F sites leads to a derepression of the E2F1 promoter in quiescent cells. The CHR-mutated promoter is activated by the E2F family of proteins (E2F1, E2F2, E2F3, and E2F4) but unable to be repressed by any of the Rb family members (Rb, p107, and p130) to the level of the wild-type promoter activity in G0, indicating that the repression by the Rb family members is required for the corepressor element. Moreover, it was shown that a factor specifically bound to the CHR element is co-purified with E2F by DNA affinity purification and co-immunoprecipitated with E2F4 and the Rb family members. These results seggested that E2F and the Rb family member proteins regulate the transcription of the E2F1 and B-myb genes by associating with an additional corepressor protein.

L24 ANSWER 12 OF 43 CAPLUS COPYRIGHT 2000 ACS
AN 1998:59274 CAPLUS
DN 128:201711
TI Stable binding to E2F is not required for the retinoblastoma protein to activate transcription, promote differentiation, and suppress tumor cell growth
AU Sellers, William R.; Novitch, Bennett G.; Miyake, Satoshi; Heith, Agnieszka; Otterson, Gregory A.; Kaye, Frederic J.; Lassar, Andrew B.; Kaelin, William G., Jr.
CS Dana-Farber Cancer Inst. & Harvard Medical School, Boston, MA, 02115, USA
SO Genes Dev. (1998), 12(1), 95-106 CODEN: GEDEEP; ISSN: 0890-9369
PB Cold Spring Harbor Laboratory Press
DT Journal
LA English
AB The retinoblastoma tumor suppressor protein (pRB) can inhibit cell cycle progression and promote differentiation. PRB interacts with a variety of transcription factors, including members of the E2F and C-EBP protein families and MyoD, and can either repress or activate transcription depending on the promoter under study. These biol. and biochem. activities of pRB have been mapped previously to a core domain, referred to as the pRB pocket. Using a panel of synthetic pRB pocket mutants, the authors found that the acute induction of a G1/S block by pRB is linked to its ability to both bind to E2F and to repress transcription. In contrast, these functions were not required for pRB to promote differentiation, which correlated with its ability to activate transcription in concert with fate-detg. proteins such as MyoD. All tumor-derived pRB mutants tested to date failed to bind to E2F and did not repress transcription. Despite an inability to bind to E2F, pRB mutants assocd. with a low risk of retinoblastoma, unlike high-risk mutants, retained the ability to activate transcription and promote differentiation. Thus, the pRB pocket participates in dual tumor suppressor functions, one linked to cell cycle progression and the other

ISSN: 0027-8424.
DT Article
LA English
AB Examination of the interactions involving transcription factor E2F activity during cell growth and terminal differentiation suggests distinct roles for Rb family members in the regulation of E2F accumulation. The major species of E2F in quiescent cells is a complex containing the E2F4 product in association with the Rb-related p130 protein. As cells enter the cell cycle, this complex disappears, and there is a concomitant accumulation of free E2F activity of which E2F4 is a major component. E2F4 then associates with the Rb-related p107 protein as cells enter S phase. Rb can be found in interactions with each E2F species, including E2F4, during G-1, but there appears to be a limited amount of Rb with respect to E2F, likely due to the maintenance of most Rb protein in an inactive state by phosphorylation. A contrasting circumstance can be found during the induction of HL60 cell differentiation. As these cells exit the cell cycle, active Rb protein appears to exceed E2F, as there is a marked accumulation of **E2F-Rb** interactions, involving all E2F species, including E2F4, which is paralleled by the conversion of Rb from a hyperphosphorylated state to a hypophosphorylated state. These results suggest that the specific ability of Rb protein to interact with each E2F species, dependent on concentration of active Rb relative to accumulation of E2F, may be critical in cell-growth decisions.

L24 ANSWER 43 OF 43 CAPLUS COPYRIGHT 2000 ACS
AN 1992:421199 CAPLUS
DN 117:21199
TI E2F transcription factor is a target for the RB protein and the cyclin A protein
AU Nevins, J. R.; Chellappan, S. P.; Mudryj, M.; Hiebert, S.; Devoto, S.; Horowitz, J.; Hunter, T.; Pines, J.
CS Dep. Microbiol. Immunol., Howard Hughes Med. Inst., Durham, NC, 27710, USA
SO Cold Spring Harbor Symp. Quant. Biol. (1991), 56(Cell Cycle), 157-62
CODEN: CSHSAZ; ISSN: 0091-7451
DT Journal; General Review
LA English
AB A review with 36 refs. Immunoassays showed that transcription factor E2F forms distinct complexes contg. cyclin A and RB protein in exts. from human monocytic cell line U937. Adenovirus E1A protein dissocd. both complexes.

L24 ANSWER 42 OF 43 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 18
AN 1991:366474 BIOSIS
TI THE E2F TRANSCRIPTION FACTOR IS A CELLULAR TARGET FOR THE RB PROTEIN.
AU CHELLAPPAN S P; HIEBERT S; MUDRYJ M; HOROWITZ J M; NEVINS J R
CS HOWARD HUGHES MED. INST., DUKE UNIVERSITY MED. CENTER, DURHAM, NORTH CAROLINA 27710.
SO CELL, (1991) 65 (6), 1053-1062.
CODEN: CELLB5. ISSN: 0092-8674.
FS BA; OLD
LA English
AB Although it is generally believed that the product of the retinoblastoma susceptibility gene (RB1) is an important regulator of cell proliferation, the biochemical mechanism for its action is unclear. We now show that the RB protein is found in a complex with the E2F transcription factor and that only the underphosphorylated form of RB is in the E2F complex. Moreover, the adenovirus E1A protein can dissociate the **E2F-RB** complex, dependent on E1A sequence also critical for E1A to bind to RB. These sequences are also critical for E1A to immortalize primary cell cultures and to transform in conjuction with other oncogenes.
Taken together, these results suggest that the interaction of RB with E2F is an important event in the control of cellular proliferation and that the dissociation of the complex is part of the mechanism by which E1A inactivates RB function.

L24 ANSWER 41 OF 43 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 17

important in cell proliferation control. E2F appears to be a functional target for the action of the tumor suppressor protein Rb that is encoded by the retinoblastoma susceptibility gene. The disruption of this **E2F-Rb** interaction, as well as a complex involving E2F in association with the cell cycle-regulated cylin A-cdk2 kinase complex, may be a common mechanism of action for the oncoproteins encoded by the DNA tumor viruses.

L24 ANSWER 38 OF 43 MEDLINE DUPLICATE 16
AN 93345762 MEDLINE
DN 93345762
TI The retinoblastoma gene: role in cell cycle control and cell differentiation.
AU Wiman K G
CS Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.
SO FASEB JOURNAL, (1993 Jul) 7 (10) 841-5. Ref: 50
Journal code: FAS. ISSN: 0892-6638.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; Cancer Journals
EM 199311
AB The retinoblastoma (RB) gene is the prototype tumor suppressor gene. It encodes a nuclear protein that acts as a cell cycle control checkpoint at the G1 phase. Deletion or inactivation of both RB alleles plays an essential, rate-limiting role in retinoblastoma and in the osteosarcomas that arise within families that carry a mutated RB gene. RB inactivation is also found in other sarcomas, small cell carcinoma of the lung, and in carcinoma of the breast, bladder, and prostate. Transforming proteins encoded by SV40, and the transforming or tumor-associated subtypes of adenoviruses and human papilloma viruses (HPV) can bind RB, thereby blocking its normal function. The EBNA-5 protein of Epstein-Barr virus (EBV) is also able to bind RB in vitro. In addition, RB can interact with several cellular proteins, including the transcription factor **E2F** . **RB** gene knock-out mice die in utero around day 14 of gestation. The embryos show disturbed neural and hematopoietic differentiation, indicating that RB is vitally important for these processes. This notion is further supported by studies demonstrating that RB expression in mouse embryo tissues is highest in cells undergoing differentiation, and that RB is required for MyoD-induced muscle differentiation.

L24 ANSWER 37 OF 43 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 15
AN 1993:228336 BIOSIS
DN PREV199395119511
TI Interactions of the p107 and Rb proteins with E2F during the cell proliferation response.
AU Schwarz, James K. (1); Devoto, Stephen H.; Smith, Eric J. (1); Chellappan,
Srikumar P.; Jakoi, Laszlo (1); Nevins, Joseph R. (1)
CS (1) Section Genetics, Howard Hughes Med. Inst., Duke University Med. Center, Durham, NC 27710 USA
SO EMBO (European Molecular Biology Organization) Journal, (1993) Vol. 12, No. 3, pp. 1013-1020.
ISSN: 0261-4189.
DT Article
LA English
AB The E2F transcription factor is found in complexes with a variety of cellular proteins including the retinoblastoma tumor suppressor protein. Various assays have demonstrated a tight correlation between the functional capacity of Rb as a growth suppressor and its ability to bind to E2F. Moreover, only the underphosphorylated form of Rb, which appears to be the active species, interacts with E2F. Despite the fact that the majority of Rb becomes hyperphosphorylated at the end of G-1, we now show that the **E2F-Rb** interaction persists through the G-1/S transition and into S phase. A distinct E2F complex does appear to be regulated in relation to the transition from G-1 to S phase. We now demonstrate that this complex contains the Rb-related p107 protein. Moreover, like the Rb protein, p107 inhibits E2F-dependent transcription in a co-transfection assay. This result, together with the observation that free, uncomplexed E2F accumulates as cells leave G-1 and enter S

CODEN: MCEBD4; ISSN: 0270-7306
DT Journal
LA English
AB The cellular transcription factor E2F appears to be a target for the regulatory action of the retinoblastoma tumor suppressor gene product. The recent isolation of the E2F1 cDNA clone, which encodes a polypeptide with properties characteristic of E2F, has now allowed a more detailed anal. of the regulation of E2F function by Rb as well as the Rb-related p107 protein and the adenovirus 19-kDa E4 gene product. Previous expts. have shown that each of these regulatory proteins can modulate the activity of cellular E2F. The authors find that each of these regulatory events can be mediated through the E2F1 product. Moreover, an examn. of various E2F1 mutations reveals distinct specificities for these regulatory proteins. For instance, the ability of E4 to alter E2F1 function is dependent upon sequences within a putative leucine repeat of E2F1 as well as within the C-terminal acidic domain. In contrast, the leucine repeat element was not important for Rb- or p107-mediated inhibition of E2F1 activity. Although the C-terminal acidic domain of E2F1, previously shown to be important for Rb binding, appears to be a site for regulation of E2F1 by Rb and p107, point mutations within this region distinguish recognition by Rb and p107. These results underscore the complexity of E2F regulatory interactions and also demonstrate a qual. distinction in the interactions of Rb and p107 with E2F1, perhaps reflective of functional differences.

d 121 4,5,7 bib ab

L21 ANSWER 4 OF 40 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:301754 BIOSIS
DN PREV199598316054
TI Cancer gene therapy: principles, problems, and perspectives.
AU Herrmann, F.
CS Dep. Med. Oncol. Applied Molecular Biol., Universitaetsklinikum Rudolf Virchow, Freie Univ. Berlin, Robert Roessle Cancer Cent., Lindenberger Weg
80, D-13122 Berlin Germany
SO Journal of Molecular Medicine (Berlin), (1995) Vol. 73, No. 4, pp. 157-163.
ISSN: 0946-2716.
DT General Review
LA English
AB Despite enormous efforts focused on the development of new drugs and the use of novel drug combinations, including high-dose regimens supported by bone marrow and blood stem cell transplantation procedures, progress in the treatment of disseminated human cancer has been marginal. Remarkable advances in our understanding of the molecular biology of cancer has provided the possibility to employ new, selective tools of genetic intervention for more successful tumor treatment. We are now witnessing the inception of gene therapy. However, gene therapists face many drawbacks, including selectivity, specificity, sensitivity, and safety of gene transfer. Despite this there are already over 70 clinical protocols accepted for genetic approaches to cancer worldwide. Strategies currently under clinical investigation and discussed here include: (a) the enhancement of tumor immunogenicity by insertion of cytokine genes, genes coding for products of the major histocompatibility complex, and those for
lymphocyte costimulatory ligands, (b) the vectoring of tumoricidal cytokines into cells that can potentially home on tumors to release their toxic products locally, (c) the use of tumor-specific prodrug activators, i.e., the insertion of enzymatically **prodrug-activating genes** fused to promoter systems which rely on differential (ideally tumor specific) transcription control, (d) gene-marking strategies which may provide new indicators for minimal, residual, and relapsed tumor disease, (e) artificial repression of gene functions by insertion of genes encoding for complementary (antisense) mRNA to the gene
of interest (e.g., oncogenes, drug resistance genes).

L21 ANSWER 5 OF 40 MEDLINE
AN 1999034927 MEDLINE
DN 99034927
TI Diffusible cytotoxic metabolites contribute to the in vitro bystander effect associated with the cyclophosphamide/cytochrome P450 2B1 cancer gene therapy paradigm.
AU Wei M X; Tamiya T; Rhee R J; Breakefield X O; Chiocca E A
CS Molecular Neurogenetics Laboratory, Department of Neurology and Neurosurgery Service, Massachusetts General Hospital, Charlestown, Massachusetts 02129, USA.
NC NS24279 (NINDS)
SO CLINICAL CANCER RESEARCH, (1995 Oct) 1 (10) 1171-7.
Journal code: C2H. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
EW 19990402
AB Tumor cells become sensitive to the inert prodrug cyclophosphamide (CPA) after transfer of the gene encoding cytochrome P450 2B1. This enzyme activates CPA into 4-hydroxycyclophosphamide, which ultimately degrades into acrolein and phosphoramide mustard, the anticancer and

prodrug is necessary and sufficient to achieve killing of the transfected cells, and medium conditioned by these cells can kill untransfected cells with similar potency. This bystander effect occurs in the presence of CPA even when only 10% of cells in culture express the P450 2B1 gene, and it is not reproduced by cells that have been irradiated. In an animal model of intracerebral brain tumors, expression of the P450 2B1 gene within the neoplastic cells enhanced significantly the antitumor effect of CPA, even when it was administered systemically. This study shows that CPA/P450 2B1 gene therapy represents a novel tumor-killing strategy that displays an expanded range of cytotoxic action both spatially and temporally within tumor cells and significantly potentiates the anticancer action of CPA when administered i.v.

L21 ANSWER 7 OF 40 MEDLINE
AN 1998289126 MEDLINE
DN 98289126
TI Gene therapy for tumors of the central nervous system.
AU Chung R Y; Chiocca E A
CS Molecular Neuro-Oncology Laboratories and Neurosurgical Service, Massachusetts General Hospital, Charlestown, Massachusetts 02129, USA.
NC CA 6924602 (NCI)
SO SURGICAL ONCOLOGY CLINICS OF NORTH AMERICA, (1998 Jul) 7 (3) 589-602. Ref: 108
Journal code: CAF. ISSN: 1055-3207.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199810
EW 19981005
AB Primary central nervous system tumors, consisting mainly of malignant gliomas, represent a unique system for the study of gene transfer techniques. Exogenous transgenes have been delivered using retroviral, adenoviral, and herpes simplex virus vectors. A number of strategies have been developed, including: (1) delivery of **prodrug activating genes**, (2) replacement of tumor suppressor genes, (3) cytokine-mediated enhancement of antitumor immune responses, and (4) antisense cDNA delivery to block the action of growth factors, cell cycle proteins, and drug resistance mechanisms. Efforts to disrupt the blood brain barrier may facilitate tumor gene delivery.

> d l27 15,17,19, 20, 29, 36, 37, bib ab

L27 ANSWER 15 OF 47 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 1
AN 1999:242624 BIOSIS
DN PREV199900242624
TI Enhanced immunogenicity of hepatitis B surface antigen by insertion of a helper T cell epitope from tetanus toxoid.
AU Chengalvala, Murty V. (1); Bhat, Ramesh A.; Bhat, Bheem M.; Vernon, Steven K.; Lubeck, Michael D.
CS (1) Discovery Research, Wyeth Ayerst Research, Philadelphia, PA, 19101 USA
SO Vaccine, (March, 1999) Vol. 17, No. 9-10, pp. 1035-1041. ISSN: 0264-410X.
DT Article
LA English
SL English
AB The currently marketed hepatitis B vaccines in the U.S. are based on the recombinant major hepatitis B surface antigen (HBsAg) of hepatitis B virus. Although a large majority of individuals develop protective immunity to HBV-induced disease after three immunizations, routinely a small but a significant percentage of the human population does not respond well to these vaccines. In this report, we describe the generation of a novel HBsAg molecule containing a Th epitope derived from tetanus toxoid (TT). Using recombinant DNA technology, the TT Th epitope (TTe) was inserted into the HBsAg coding sequence. Using a **recombinant adenovirus** expression system, HBsAg-TTe chimeric protein was produced in **A549 cells** and found to be secreted into culture medium as 22 nm particles. The chimeric HBsAg particles were readily purified by immunoaffinity chromatography and their immunogenicity was evaluated relative to native HBsAg produced in an adenovirus expression system. When evaluated in inbred and outbred strains of mice, HBsAg-TTe was shown to enhance several-fold the anti-HBs response relative to native HBsAg. Further enhanced responses were observed in mice primed with TT. This highly immunogenic form of HBsAg has promise as an improved HBsAg subunit vaccine.

L27 ANSWER 17 OF 47 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 2
AN 1999:505100 BIOSIS
DN PREV199900505100
TI Interleukin-1 receptor antagonist inhibits interleukin-8 expression in A549 respiratory epithelial cells infected in vitro with a replication-deficient **recombinant adenovirus** vector.
AU Schwarz, Yehuda A. (1); Amin, Raouf S.; Stark, James M.; Trapnell, Bruce C.; Wilmott, Robert W.
CS (1) Division of Pulmonary Medicine, Tel-Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv, 64239 Israel
SO American Journal of Respiratory Cell and Molecular Biology, (Sept., 1999) Vol. 21, No. 3, pp. 388-394. ISSN: 1044-1549.
DT Article
LA English
SL English
AB In an earlier study, we showed that a **recombinant adenovirus** vector with deletions in the E1 and E3 regions of the viral genome (AV1LacZ4) induces expression of interleukin (IL)-8 in **A549 cells** (a human respiratory cell line). IL-8 can be induced through several pathways, including activation by IL-1. We tested the hypothesis that the induction of IL-8 by the AV1LacZ4 adenovirus is accomplished by means of the IL-1/IL-8 activation pathway, which could be blocked by IL-1 receptor antagonist (IRAP). Viral infections of **A549 cells** were performed at a multiplicity of infection

by virus vector-infected cells, partly through IL-6 activation that can be downregulated by IRAP.

L27 ANSWER 19 OF 47 CAPLUS COPYRIGHT 2000 ACS
AN 1999:433333 CAPLUS
DN 131:238480
TI Construction and identification of replication-deficient human thrombopoietin **recombinant adenoviruses**
AU Liu, Lin; Luo, Chengji; Su, Yongping
CS Xinqiao Hospital, Third Military Medical University, Chungking, 400037, Peop. Rep. China
SO Di-San Junyi Daxue Xuebao (1999), 21(5), 314-317
CODEN: DYXUE8; ISSN: 1000-5404
PB Di-San Junyi Daxue
DT Journal
LA Chinese
AB The authors constructed replication-deficient human thrombopoietin (TPO) **recombinant adenoviruses** (AdCMVTPO). The full-length human TPO cDNA was cloned down stream of human CMV promoter of adenoviral shuttle plasmid pCA3. Then the resultant pCA3-TPO plasmid was cotransfected into 293 cells with the plasmid pBHG10 carrying the adenoviral genome. Plasmid AdCMVTPO was successfully generated with homologous recombination. **A549 cells** were infected with AdCMVTPO and the expression of human TPO was evaluated in vivo. The titer of AdCMVTPO reached 4.5 .times. 109 pfu/mL after amplification in 293 cells. **A549 cells** expressed high level of human TPO after infection. The **recombinant adenovirus** maybe used in the gene therapy of hemopoietic reconstruction.

L27 ANSWER 20 OF 47 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 3
AN 1999:121708 BIOSIS
DN PREV199900121708
TI Upregulation of fibrinolysis by adenovirus-mediated transfer of urokinase-type plasminogen activator genes to lung cells in vitro and in vivo.
AU Hattori, Noboru; Sisson, Thomas H.; Xu, Yin; Simon, Richard H. (1)
CS (1) Univ. Michigan Med. Cent., 6301 Medical Science Research Build. 3, Box 0642, Ann Arbor, MI 48109-0642 USA
SO Human Gene Therapy, (Jan. 20, 1999) Vol. 10, No. 2, pp. 215-222.
ISSN: 1043-0342.
DT Article
LA English
AB Impaired fibrinolytic activity within the lungs is a common manifestation of acute and chronic inflammatory lung diseases. Our previous work using transgenic mice showed that upregulation of fibrinolysis reduced pulmonary fibrosis following bleomycin-induced inflammatory lung injury. As a strategy to accelerate fibrinolysis, we generated **recombinant adenoviruses** containing human and mouse urokinase-type plasminogen activator (uPA) cDNAs. Both vectors induced the expression of functional uPA in human lung-derived epithelial **A549 cells**. A single intratracheal instillation of these uPA-containing adenoviruses into mouse lungs resulted in increased plasminogen activator activity in bronchoalveolar lavage fluid for at least 2 weeks. Plasma-derived fibrin-rich matrices overlaid on **A549 cells** infected with these uPA vectors were lysed efficiently in a dose-dependent fashion. Similarly, fibrin matrices formed within intact lungs that had been infected with these uPA-containing adenoviruses were also lysed more rapidly compared with noninfected and control virus-infected lungs. These results indicate that adenovirus-mediated transduction of uPA successfully upregulates fibrinolysis in vitro and in vivo. These uPA vectors can be readily used for testing the role of the fibrinolytic system in animal models of lung fibrosis, with particular attention to their therapeutic potential.

L27 ANSWER 29 OF 47 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 5
AN 1998:211051 BIOSIS
DN PREV199800211051
TI Adenovirus-mediated expression of an elastase-specific inhibitor

chosen to drive the synthesis of elafin: the small (380 bp) human cytomegalovirus promoter (HCMV), the Ad2 major late promoter (MLP) and the mouse cytomegalovirus (MCMV) promoter. Human alveolar epithelial cells (A549), as well as rat and human primary pulmonary fibroblasts were infected with Ad5-HCMV-EL, Ad5-MLP-EL, Ad5-MCMV-EL and with the control Ad5-dl70/3. The MCMV promote was the most efficient promoter in all cells studied. MLP was the least efficient promoter. Intermediate between MCMV and MLP was HCMV which was able to induce significant amounts of elafin, particularly in human **A549 cells**. When compared in vivo in rat lungs, results were similar; MCMV was the only promoter which induced significant amounts of elafin as assessed by Northern blot analysis and ELISA, even with a low dose of virus (3 X 108 p.f.u.). Our data indicate that the MCMV promoter is the promoter of choice for the strong induction of adenovirus-mediated transgenes in the lung, and suggest its suitability both in rodent experimental models and in humans for investigative and therapeutic purposes.

L27 ANSWER 36 OF 47 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 8
AN 1996:326521 BIOSIS
DN PREV199699048877
TI Elimination of both E1 and E2a from adenovirus vectors further improves prospects for in vivo human gene therapy.
AU Gorziglia, Mario I.; Kadan, Michael J.; Yei, Soonpin; Lim, Jin; Lee, Gai M.; Luthra, Rajni; Trapnell, Bruce C. (1)
CS (1) Genetic Therapy Inc., 948 Clopper Rd., Gaithersburg, MD 20878 USA
SO Journal of Virology, (1996) Vol. 70, No. 6, pp. 4173-4178. ISSN: 0022-538X.
DT Article
LA English
AB A novel **recombinant adenovirus** vector, Av3nBg, was constructed with deletions in adenovirus E1, E2a, and E3 regions and expressing a beta-galactosidase reporter gene. Av3nBg can be propagated at a high titer in a corresponding A549-derived cell line, AE1-2a, which contains the adenovirus E1 and E2a region genes inducibly expressed from separate glucocorticoid-responsive promoters. Av3nBg demonstrated gene transfer and expression comparable to that of Av1nBg, a first-generation adenovirus vector with deletions in E1 and E3. Several lines of evidence suggest that this vector is significantly more attenuated than E1 and E3 deletion vectors. Metabolic DNA labeling studies showed no detectable de novo vector DNA synthesis or accumulation, and metabolic protein labeling demonstrated no detectable de novo hexon protein synthesis for Av3nBg in naive **A549 cells** even at a multiplicity of infection of up to 3,000 PFU per cell. Additionally, naive **A549 cells** infected by Av3nBg did not accumulate infectious virions. In contrast, both Av1nBg and Av2Lu vectors showed DNA replication and hexon protein synthesis at multiplicities of infection of 500 PFU per cell. Av2Lu has a deletion in E1 and also carries a temperature-sensitive mutation in E2a. Thus, molecular characterization has demonstrated that the Av3nBg vector is improved with respect to the potential for vector DNA replication and hexon protein expression compared with both first-generation (Av1nBg) and second-generation (Av2Lu) adenoviral vectors. These observations may have important implications for potential use of adenovirus vectors in human gene therapy.

L27 ANSWER 37 OF 47 MEDLINE DUPLICATE 9
AN 97041567 MEDLINE
DN 97041567
TI Infection of **A549 cells** with a **recombinant adenovirus** vector induces ICAM-1 expression and increased CD-18-dependent adhesion of activated neutrophils.
AU Stark J M; Amin R S; Trapnell B C
CS Children's Hospital Medical Center, Cincinnati, OH 45229, USA.
NC HL51832 (NHLBI)
K08-HL02505 (NHLBI)
SO HUMAN GENE THERAPY, (1996 Sep 10) 7 (14) 1669-81. Journal code: A12. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

delivery to the airway epithelium of CF patients. However, studies in animal models using these AV vectors demonstrate pulmonary inflammation following AV exposure. Using an in vitro model, we examined the hypothesis that exposure of respiratory epithelial cells to AV vectors results in upregulation of ICAM-1 gene expression. Infections were performed using a replication-deficient, first-generation AV vector. **A549 cells** (a human pulmonary adenocarcinoma cell line) were exposed to AV at multiplicity of infection of 50-150 plaque-forming units/cell (resulting in > 90% of cells expressing the reporter gene by 48 hr following exposure). Measurements of ICAM-1 expression were made at time intervals following virus exposure using enzyme immunoassay, flow cytometry, and Northern blot analysis. Cell-bound ICAM-1 was significantly increased 96 hr following vector exposure, two to four times control, $p < 0.001$). The AV-exposed **A549 cells** also supported increased levels of adhesion of activated neutrophils 96 hr following AV exposure (four times control, $p < 0.001$) that was blocked by antibody to CD18. AV exposure of A549 monolayers increases expression of biologically active ICAM-1. Strategies to minimize host cellular proinflammatory responses to the replication-deficient AV vectors may improve their safety for gene therapy.

p53con

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d 130 1-15 bib

L30 ANSWER 1 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 1
AN 1999:508929 BIOSIS
DN PREV199900508929
TI Effect of p53 protein redox states on binding to supercoiled and linear DNA.
AU Fojta, Miroslav; Kubicarova, Tatiana; Vojtesek, Borivoj; Palecek, Emil (1)
CS (1) Institute of Biophysics, Academy of Sciences of the Czech Republic, Kralovopolska 135, CZ-612 65, Brno Czech Republic
SO Journal of Biological Chemistry, (Sept. 3, 1999) Vol. 274, No. 36, pp. 25749-25755.
ISSN: 0021-9258.
DT Article
LA English
SL English

L30 ANSWER 2 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 2
AN 1999:342184 BIOSIS
DN PREV199900342184
TI Effect of transition metals on binding of p53 protein to supercoiled DNA and to consensus sequence in DNA fragments.
AU Palecek, Emil (1); Brazdova, Marie; Cernocka, Hana; Vlk, Daniel; Brazda, Vaclav; Vojtesek, Borivoj
CS (1) Institute of Biophysics, Academy of Sciences of the Czech Republic, Kralovopolska 135, 612 65, Brno Czech Republic
SO Oncogene, (June 17, 1999) Vol. 18, No. 24, pp. 3617-3625.
ISSN: 0950-9232.
DT Article
LA English
SL English

L30 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2000 ACS
AN 1999:774950 CAPLUS
TI DNA Bending Due to Specific p53 and p53 Core Domain-DNA Interactions Visualized by Electron Microscopy
AU Cherny, Dmitry I.; Striker, George; Subramaniam, Vinod; Jett, Stephen D.; Palecek, Emil; Jovin, Thomas M.
CS Department of Molecular Biology, Max Planck Institute for Biophysical Chemistry, Gottingen, D-37077, Germany
SO J. Mol. Biol. (1999), 294(4), 1015-1026
CODEN: JMOBAK; ISSN: 0022-2836
PB Academic Press
DT Journal
LA English

L30 ANSWER 4 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 3
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DN PREV199900069484
TI Poly(ADP-ribosyl)ation is required for p53-dependent signal transduction induced by radiation.
AU Wang, Xinjiang; Ohnishi, Ken; Takahashi, Akihisa; Ohnishi, Takeo (1)
CS (1) Dep. Biology, Nara Med. Univ., Kashihara, Nara 634-8521 Japan
SO Oncogene, (Dec. 3, 1998) Vol. 17, No. 22, pp. 2819-2825.
ISSN: 0950-9232.
DT Article
LA English

L30 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2000 ACS
AN 1995:939578 CAPLUS
DN 124:47420
TI The first intron of human H-ras is regulated by p53: Mediation of specific
activation by a p53-binding element
AU Zhang, Wei; Randhawa, Guryaneet S.; Gau, Jyh-Pyng; Shay, Jerry W.;

CS UT M.D. Anderson Cancer Center, Houston, TX 77030
SO Proc Annu Meet Am Assoc Cancer Res, (1994). Vol. [redacted], pp. A3579.
ISSN: 0197-016X.
DT (MEETING ABSTRACTS)
FS ICDB; L
LA English
EM 199502

L30 ANSWER 7 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:498624 BIOSIS
DN PREV199497511624
TI Specific DNA binding by p53 is independent of mutation at serine 389, the casein kinase II site.
AU Rolley, Nicky; Milner, Jo (1)
CS (1) Dep. Biol., Univ. York, York YO1 5DD UK
SO Oncogene, (1994) Vol. 9, No. 10, pp. 3067-3070.
ISSN: 0950-9232.
DT Article
LA English

L30 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2000 ACS
AN 1994:501099 CAPLUS
DN 121:101099
TI A temperature-sensitive mutant of human p53
AU Zhang, Wei; Guo, Xiang Yang; Hu, Gui Ying; Liu, Wen Biao; Shay, Jerry W.; Deisseroth, Albert B.
CS M. D. Anderson Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SO EMBO J. (1994), 13(11), 2535-44
CODEN: EMJODG; ISSN: 0261-4189
DT Journal
LA English

L30 ANSWER 9 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 4
AN 1994:449530 BIOSIS
DN PREV199497462530
TI The requirement of the carboxyl terminus of p53 for DNA binding and transcriptional activation depends on the specific p53 binding DNA element.
AU Zhang, Wei; Guo, Xiang-Yang D.; Deisseroth, Albert B. (1)
CS (1) Dep. Hematol., Univ. Texas M. D. Anderson Cancer Cent., Houston, TX 77030 USA
SO Oncogene, (1994) Vol. 9, No. 9, pp. 2513-2521.
ISSN: 0950-9232.
DT Article
LA English

L30 ANSWER 10 OF 15 CANCERLIT
AN 94602763 CANCERLIT
DN 94602763
TI Cellular proteins associate with the conformational domain of p53 and enhance its sequence-specific DNA-binding activity (Meeting abstract).
AU Srinivasan R; Roth J A; Maxwell S A
CS Dept. of Thoracic and Cardiovascular Surgery, UT M.D. Anderson Cancer Center, Houston, TX 77030.
SO Proc Annu Meet Am Assoc Cancer Res, (1994). Vol. 35, pp. A1077.
ISSN: 0197-016X.
DT (MEETING ABSTRACTS)
FS ICDB; L
LA English
EM 199411

L30 ANSWER 11 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 5
AN 1994:162501 BIOSIS
DN PREV199497175501
TI Distinct regions of p53 have a differential role in transcriptional activation and repression functions.
AU Sang, Bi-Ching; Chen, Jeou-Yuan; Minna, John; Barbosa, Miguel S. (1)
CS (1) Dep. Microbiology, University Texas Southwestern Medical Center at Dallas, Dallas, TX 75235 USA
SO Oncogene, (1994) Vol. 9, No. 3, pp. 853-859.
ISSN: 0950-9232.
DT Article
LA English

DT Article
LA English

L30 ANSWER 13 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 7
AN 1993:587640 BIOSIS
DN PREV199497007010
TI Inactive p53 mutants may enhance the transcriptional activity of wild-type
p53.
AU Zhang, Wei; Shay, Jerry W.; Deisseroth, Albert (1)
CS (1) Dep. Hematol., Box 24, Univ. Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030 USA
SO Cancer Research, (1993) Vol. 53, No. 20, pp. 4772-4775.
ISSN: 0008-5472.
DT Article
LA English

L30 ANSWER 14 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 8
AN 1993:499584 BIOSIS
DN PREV199396123591
TI Novel DNA binding of p53 mutants and their role in transcriptional activation.
AU Zhang, Wei; Funk, Walter D.; Wright, Woodring E.; Shay, Jerry W.; Deisseroth, Albert B. (1)
CS (1) Dep. Hematol., Box 24, Univ. Tex. M. D. Anderson Cancer Cent., 1515 Holcombe Blvd., Houston, TX 77030 USA
SO Oncogene, (1993) Vol. 8, No. 9, pp. 2555-2559.
ISSN: 0950-9232.
DT Article
LA English

L30 ANSWER 15 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 9
AN 1993:411580 BIOSIS
DN PREV199396077305
TI Heterogeneity of transcriptional activity of mutant p53 proteins and p53 DNA target sequences.
AU Chen, Jeou-Yuan (1); Funk, Walter D.; Wright, Woodring E.; Shay, Jerry W.;
Minna, John D.
CS (1) Simmons Cancer Cent. Dep. Internal Med., Dallas, TX 75235-8590 USA
SO Oncogene, (1993) Vol. 8, No. 8, pp. 2159-2166.
ISSN: 0950-9232.
DT Article
LA English